REMARKS

I. Status of the Claims

Claims 59-109 are pending in the application and are canceled herein. New claims 110-155 are added and are presented in Appendix A. The new claims are supported by the previously pending claims and differ from those claims primarily in that they have been amended to recite use of hyaluronic acid and derivatives thereof. Consideration of these new claims in view of the following comments is respectfully requested.

II. Formalities

The examiner has requested a substitute sequence listing, CRF and statement of conformity, which is enclosed. The examiner also has requested a new substitute specification. Applicants are in the process of preparing such and it will be submitted shortly.

Applicants have provided new claims 110-155 to address the inconsistencies in previous amendments. Applicants are in the process of collecting copies of references to be submitted in an IDS.

III. Rejections Under 35 U.S.C. §112

A. First Paragraph

The examiner has objected to claims directed to "Ad.RSV.αVEGF" and "Ad.VA1.αVEGF" as not supported by the specification, which instead refers to "Ad.RSV.aVEGF" and "Ad.VA1.aVEGF." Applicants respectfully traverse. These clearly are

the same vectors, with a simple text formatting error having arisen with the submission of a new specification. That this is true can be gleaned from page 20, bottom paragraph, where "β" and "b" are used interchangeably. Finally, one of skill in the art would recognize αVEGF as the appropriate nomenclature, and that "a" and "α" often are used interchangeably in the field of biology. Reconsideration and withdrawal of the rejection is respectfully requested.

B. Second Paragraph

The examiner has objected to claim 65 for the recitation of "the vector is a liposome." Claim 65 has been canceled and the new claims do not contain a similar recitation. Reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejections Under 35 U.S.C. §102

A. U.S. Patent 6,037,329 ("the '329 patent")

Claims 59-61, 63, 104, 106 and 107 are rejected under §102 as anticipated by the '329 patent, which is said to disclose compositions for the treatment of cells using nucleic acids encoding protein and antisense and, further, to include hyaluronic acid. Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled. All of these claims have been canceled, but applicants submit the following to the extent that the reference would be considered relevant to any of the new claims.

In the abstract, the '329 patent states that it relates to the preparation of "conjugates of a receptor-binding internalized ligand and a cytocide-encoding agent." In particular "the conjugates contain a polypeptide that is reactive with an FGF receptor." In column 1, lines 18 to

23, it is further stated that the invention "relates to the treatment of diseases." Column 47, line 34 states that "the conjugates and complexes provided herein are useful for the treatment and prevention of various diseases." Column 48 then lists a large number of conditions from diabetes to colon carcinoma and from toxic eczema to varicose veins.

Applicant submits that the disclosure of the use of the conjugates for ophthalmic diseases merely forms one of the plethora of diseases disclosed. There is no evidence or experimental support that teaches the use of the claimed conjugates in ophthalmic conditions. In addition, column 48, line 66 to column 49, line 4 states that "for the ophthalmic uses herein, local administration, either by topical administration or by injection is preferred" and "conjugates and complexes are mixed with a suitable pharmaceutical carrier or vehicle." However, there is no specific teaching of any particular carrier or vehicle, although column 50 refers to a large number of various agents including water, polyethylene glycol, glycerine, *etc.* Apart from one oblique reference at lines 55 to 56 of column 50, namely, "The ophthalmic compositions *may also* include additional components, such as hyaluronic acid," there is no reference to hyaluronic acid anywhere in the specification. More importantly, there is no teaching or data showing that hyaluronic acid could be used or would in fact assist in the use of the claimed conjugates. Indeed, the applicants can find no reference to hyaluronic acid in the 208 columns of specification except for the reference indicated in column 50. Therefore, it is respectfully submitted that the '329 patent does not teach the use of hyaluronic acid in ophthalmic treatments, but merely includes reference to its use in passing, much in the same way it refers to many other compounds, compositions and components.

More importantly, the '329 patent does not relate to gene therapy using antisense treatment. The composition disclosed in the '329 patent is for *in vivo* expression. The nucleic acid of interest is fused to a polypeptide which is capable of binding to the FGF receptor on the surface of a cell such that the entire composition is internalized into the cell. Once inside the cell the nucleic acid of interest, which preferably encodes a cytocide-agent, is presumably transcribed and translated. In other words, the '329 patent does not contemplate an antisense therapy for ophthalmic conditions, but merely relates to a process, and a composition useful for the process, of getting a DNA construct into a cell. Hyaluronic acid is not part of their invention, but is there merely as an agent that ***may*** also be used. Accordingly, applicants consider that the '329 patent does not teach or suggest the use of hyaluronic acid for ophthalmic treatment, and in particular does not even remotely contemplate the use of hyaluronic acid and antisense therapy for ophthalmic conditions.

Reconsideration and withdrawal of the rejection is respectfully requested.

B. U.S. Patents 5,710,136 ("the '136 patent"); 5,731,294 ("the '294 patent"); 5,639,736 ("the '736 patent"); 5,814,620 ("the '620 patent") and 5,801,156 ("the '156 patent")

Claims 75, 76, 78-82, 94, 95 and 97-99 stand rejected as anticipated by U.S. Patents 5,710,136, 5,731,294, 5,639,736, 5,814,620 and 5,801,156. According to the examiner, these patents each "disclose antisense oligonucleotides targeted to VEGF [and] methods of treating ocular as well as neovascular disease." Applicants traverse, but the rejected claims have been canceled. To the extent that that the references would be considered relevant to any of the new claims, applicants provide the following.

Each of the cited patents fails to disclose the use of hyaluronic acid and a nucleic acid for the treatment of retinal disease mediated by abnormal neovascularization, as now recited by the claims. There is no disclosure that gene therapy *per se* could correct or at least alleviate the problems of neovascularization. Not withstanding this point, new claims 142 to 155 now recite a nucleic acid sequence corresponding to at least a part of the sequence encoding VEGF. In other words, not only do the claims require the use of hyaluronic acid ***and*** a sequence encoding VEGF, but this also must be useful for the treatment of retinal disease mediated by abnormal neovascularization.

To the contrary, the cited patents merely disclose the use of viruses for the introduction of DNA into target cells. The citations do not suggest that recombinant viruses can be used for *in situ* production of antisense sequences for integration of an anti-sense sequence into the genome of the target cell, and they certainly do not disclose a composition comprising a *recombinant virus* comprising an anti-sense nucleic acid sequence corresponding to at least a part of the sequence encoding VEGF, and one or ***more adjuvants one of which is hyaluronic acid or a derivative thereof***. In contrast, the present specification clearly states that viruses are used for production of anti-sense DNA within the target cell as set out at page 14, paragraph 3, and to facilitate integration of an anti-sense construct into the cellular genome, at page 14, paragraph 4. Accordingly, the present claims are both novel and inventive over the cited art.

Reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. §103

A. U.S. Patent 5,660,851

The examiner has rejected claims 59-62, 65, 77, 96 and 100 over the '156 patent, the '620 patent, the '736 patent, the '136 patent and the '329 patent, further in view of U.S. Patent 5,660,851 ("the '851 patent"). Applicants traverse, but all of the rejected claims have been canceled. Applicants provide the following discussion of the '851 patent to the extent the examiner believes the rejection may bear on the claims now pending.

The deficiencies of the other references used in the rejection have been discussed above. The '851 patent relates to absorbable ocular inserts that may be used to deliver a wide range of drugs to the eye. See column 1, lines 11 to 14. However, there is no disclosure or teaching of the treatment of neovascularization. Moreover, there is no disclosure or teaching of antisense therapy for the treatment of neovascularization, and the only mention of hyaluronic acid is an oblique reference in column 13, line 39 and in claim 11.

Further, the ocular insert is described in column 6 lines 27 to 33 as being used to deliver water soluble or water insoluble drugs such as nonsteroidal anti-inflammatory compounds, anesthetics, chemotherapeutic agents, immunosuppressive agents, steroids, antibiotics, anti-virals, antifungals, steroidal anti-inflammatories, and anticoagulants. There is no mention of antisense therapy. Indeed, given the wide range of "drugs" encompassed, a person skilled in the art would not be directed to the use of antisense constructs.

Applicants' position is further supported in column 8, line 14 to column 9, line 53. The '851 patent there discloses an exhaustive list of "biologically acceptable substances, including a biologically active materials, that can be delivered using these methods and compositions." However, even though the list of agents includes many carboxylic acid-containing bioactive compounds are described, for example, in The Merck Index, 14th edition, (Merck & Co., Inc. New Jersey, 1989) there is no disclosure of antisense therapy. Indeed, even when the '851 patent discusses drugs used to treat the eye and surrounding tissues (column 9, lines 3 to 53), there is no mention of antisense therapy, neovascularization or hyalyuronic acid.

The only mention of hyaluronic acid is found in Section VI, entitled "Preparation of Ocular Insert"; however, this section relates to the manufacture of the actual insert not to the delivery of any particular compound or composition. For example, column 13, lines 30 to 41 state:

> The polymeric materials of embodiments A, B, and C, can be used as is to form ocular inserts, or, alternatively, can be mixed with other polymers...including... polyglycolic acid, collagen, polyorthoesters, polylactic acid, cellulose ester derivatives, dextran and its derivatives, albumin, gelatin, *hyaluronic acid*, amylose and its derivatives, poly(vinyl alcohol), maleic anhydride derivatives, and polyphosphazenes.

Again, hyaluronic acid is merely part of a laundry list of possible polymers that may be used. There is no evidence that hyaluronic acid was ever used by the inventors of the '851 patent, and there certainly is no teaching that hyaluronic acid may be a useful agent to deliver antisense therapy for the treatment of neovascularization. Therefore, applicants submit that the '851 patent would not in any way motivate a person skilled in the art to use hyaluronic acid for delivering antisense therapy to the eye.

Reconsideration and withdrawal of the rejection is respectfully requested.

B. U.S. Patent 5,624,803

The examiner has rejected claims 62-64, 66-71, 73, 74, 83-93 and 100-109 over the '156 patent, the '620 patent, the '736 patent, the '136 patent, the '329 patent, and the '851 patent, further in view of U.S. Patent 5,624,803 ("the '803 patent"). Applicants traverse, but all of the rejected claims have been canceled. Applicants provide the following discussion of the '803 patent to the extent the examiner believes the rejection may bear on the claims now pending.

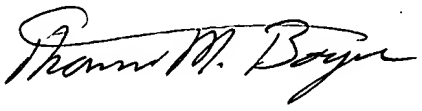
The deficiencies of the other references used in the rejection have been discussed above. The '803 patent relates to methods and materials for delivering antisense, triplex and/or ribozyme oligonucleotides intracellularly. It does ***not*** relate to neovascularization, hyaluronic acid or methods of treating ophthalmic conditions with antisense VEGF oligonucleotides in combination with hyaluronic acid. The '803 patent provides only general background information that might be of interest to a person skilled in the art wishing to use antisense. There certainly is no motivation to combine the teachings of the '803 patent with any of the other cited art. Indeed, there is no teaching that the disclosed antisense delivery methods would actually work for ophthalmic conditions. Applicants therefore believes that the '803 patent is irrelevant to the presently claimed invention.

Reconsideration and withdrawal of the rejection is respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notice to that effect is earnestly solicited. Should Examiner McGarry have any questions regarding this submission, a telephone call to the undersigned is invited. Please date stamp and return the enclosed postcard as evidence of receipt.

Very truly yours,



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APPENDIX A - MARKED UP COPY OF AMENDED CLAIMS

110. (New) A composition, comprising:

a nucleic acid comprising a polynucleotide selected from the group consisting of a polynucleotide which is anti-sense to a target polynucleotide and/or a sense polynucleotide encoding a protein;

an adjuvant selected from the group consisting of hyaluronic acid and derivatives thereof; and

a pharmaceutically acceptable carrier.

111. (New) The composition of claim 110, wherein the nucleic acid comprises a polynucleotide which is anti-sense to a target polynucleotide.

112. (New) The composition of claim 111, wherein the target polynucleotide is selected from the group consisting of genomic DNA, cDNA, messenger RNA (mRNA) and an oligonucleotide.

113. (New) The composition of claim 110, wherein the nucleic acid is operatively linked to a vector.

114. (New) The composition of claim 113, wherein the polynucleotide linked to the vector comprises a sense polynucleotide encoding a protein.

115. (New) The composition of claim 113, wherein the polynucleotide linked to the vector comprises an anti-sense polynucleotide.

116. (New) The composition of claim 113, wherein the vector is a virus.

117. (New) The composition of claim 116, wherein the virus is selected from the group consisting of adenoviruses, adeno-associated viruses, herpes viruses and retroviruses.

117. (New) The composition of claim 116, wherein the virus is a replication-defective adenovirus.

118. (New) The composition of claim 117, where the replication-defective adenovirus comprises a promoter selected from the group consisting of a respiratory syncytial virus promoter, a cytomegalovirus promoter, an adenovirus major late protein (MLP), and VA1 pol III and β-actin promoters.

119. (New) The composition of claim 118, wherein the replication-detective adenovirus comprises a promoter selected from the group consisting of a respiratory syncytial virus promoter and a cytomegalovirus promoter.

120. (New) The composition of claim 113, wherein the vector is selected from the group consisting of pAd.RSV, pAd.MLP and pAdVA1.

121. (New) The composition of claim 113, wherein the vector is selected from the group consisting of Ad.RSV.αVEGF and AdVA1αVEGF.

122. (New) The composition of claim 113, wherein the vector further comprises a polyadenylation signal sequence.

123. (New) The composition of claim 122, wherein the polyadenylation signal sequence comprises an SV40 signal sequence.

124. (New) A composition comprising a nucleic acid comprising:

a polynucleotide of 7 to 50 nucleotides long, which is anti-sense to at least a portion of a polynucleotide encoding a vascular endothelial growth factor (VEGF);

and a pharmaceutically-acceptable carrier.

125. (New) The composition of claim 124, further comprising an adjuvant selected from the group consisting of adjuvants which increase cellular uptake.

126. (New) The composition of claim 125, wherein the adjuvant is selected from the group consisting of hyaluronic acid and derivatives thereof.

127. (New) The composition of claim 124, wherein the anti-sense polynucleotide has 148% complementarity to a portion of the gene encoding VEGF.

128. (New) The composition of claim 124, wherein the anti-sense polynucleotide is 16 to 50 nucleotides long.

129. (New) The composition of claim 128, wherein the anti-sense polynucleotide is from 7 to 22 nucleotides long.

130. (New) The composition of claim 128, wherein the anti-sense polynucleotide is from 7 to 19 nucleotides long.

131. (New) The composition of claim 124, wherein:

the nucleic acid is operatively linked to a viral vector; and

the anti-sense polynucleotide is from about 20 nucleotides long to the full length of the sense polynucleotide encoding VEGF.

132. (New) The composition of claim 124, further comprising an adjuvant.

133. (New) The composition of claim 124, wherein the adjuvant is selected from the group

consisting of hyaluronic acid and derivatives thereof.

134. (New) The composition of claim 124, wherein the anti-sense polynucleotide is from about 50 nucleotides long to the full length sense polynucleotide encoding VEGF.

135. (New) The composition of claim 131, wherein the sense polynucleotide encodes a VEGF selected from the group consisting of human retinal pigment epithelial cell VEGF and human choroidal endothelial cell VEGF.

136. (New) A composition comprising:

a virus operatively linked to a nucleic acid comprising a polynucleotide which is complementary to a sense polynucleotide encoding at least a portion of a vascular endothelial growth factor (VEGF), the virus being capable of integrating the anti-sense polynucleotide into the genome of a target cell; and

a pharmaceutically-acceptable carrier.

137. (New) The composition of claim 136, further comprising an adjuvant.

138. (New) The composition of claim 137, wherein the adjuvant is selected from the group consisting of hyaluronic acid and derivatives thereof.

139. (New) The composition of claim 136, wherein the virus is an adeno-associated virus.

140. (New) The composition of claim 136, wherein the anti-sense polynucleotide is from about 20 nucleotides long to the full length VEGF-encoding sense polynucleotide.

141. (New) The composition of claim 140, wherein the anti-sense polynucleotide is at least about 50 nucleotides long.

142. (New) A method of treating a retinal disease associated with abnormal neovascularization, comprising administering a composition comprising an amount of a nucleic acid comprising a polynucleotide which is anti-sense to at least a portion of a sense polynucleotide encoding a vascular endothelial growth factor (VEGF), and one or more adjuvants for increasing cellular uptake, wherein said adjuvants includes at least hyaluronic acid or derivatives thereof into the eye(s) of a subject in need of such treatment, effective to inhibit or reduce neovascularization.

143. (New) The method of claim 142, wherein the anti-sense polynucleotide is 7 to 50 nucleotides long.

144. (New) The method of claim 143, wherein the anti-sense polynucleotide is at least 16 nucleotides long.

145. (New) The method of claim 144, wherein the anti-sense polynucleotide is up to 22 nucleotides long.

146. (New) A method of treating a retinal disease associated with abnormal neovascularization, comprising the acute administration to a subject in need of such treatment of a composition comprising:

a nucleic acid comprising a polynucleotide selected from the group consisting of a polynucleotide which is anti-sense to a target polynucleotide and/or a sense polynucleotide encoding a protein, wherein said polynucleotide is operatively linked to a vector;

an adjuvant selected from the group consisting of hyaluronic acid and derivatives thereof; and

a pharmaceutically acceptable carrier,

in an amount of the nucleic acid effective to inhibit or reduce abnormal neovascularization.

147. (New) A long-term method of treating a retinal disease associated with abnormal neovascularization, comprising chronically administering to the eye(s) of a subject in need of such treatment a composition comprising:

a virus operatively linked to a nucleic acid comprising a polynucleotide which is complementary to a sense polynucleotide encoding at least a portion of a vascular endothelial growth factor (VEGF), the virus being capable of integrating the anti-sense polynucleotide into the genome of a target cell; and

a pharmaceutically-acceptable carrier,

in an amount of the nucleic acid effective to inhibit or reduce neovascularization.

148. (New) A long-term method of treating a retinal disease associated with abnormal neovascularization, comprising chronically administering into the eye(s) of a subject in need of such treatment a composition comprising

a virus operatively linked to a nucleic acid comprising a polynucleotide which is complementary to a sense polynucleotide encoding at least a portion of a vascular endothelial growth factor (VEGF), the virus being capable of integrating the anti-sense polynucleotide into the genome of a target cell; and

a pharmaceutically-acceptable carrier,

in an amount of the nucleic acid effective to inhibit or reduce neovascularization.

149. (New) The method of claim 142, wherein the retinal disease is selected from the group consisting of age-related macular degeneration, diabetic retinopathy, branch or central

retinal vein occlusion, retinopathy of prematurity, rubeosis iridis and corneal neovascularization.

150. (New) A method of promoting uptake of an exogenous nucleic acid by a target cell, comprising contacting a target cell with a nucleic acid or with a virus or vector operatively linked to the nucleic acid, in the presence of an adjuvant selected from the group consisting of hyaluronic acid and derivatives thereof.

151. (New) The method of claim 150, wherein the target call is a phagocytic cell.

152. (New) The method of claim 150, wherein the nucleic acid, the virus or the vector, and the adjuvant are contacted with the cell *in vitro*.

153. (New) The method of claim 152, wherein the nucleic acid and the adjuvant are contacted with the cell in the form of a composition.

154. (New) The method of claim 152, wherein the nucleic acid, the virus or the vector, and the adjuvant are administered to a subject *in vivo*.

155. (New) The method of claim 154, wherein the nucleic acid, the virus or the vector, and the adjuvant are administered to the subject in the form of a composition.